UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,842	11/17/2000	Roger Briesewitz	STAN-131	8224

24353 7590 06/13/2003

BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 06/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,842	BRIESEWITZ ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,22-26,30-34 and 36-38* is/are pending in the application.

4a) Of the above claim(s) *1-15, and 37-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18,22-26,30-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1 ☐ Certified copies of the priority documents have been received.

2 ☐ Certified copies of the priority documents have been received in Application No. _____ .

3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-18, 22-26, 30-34 and 36-38 are pending.

2. Claims 1-15 and 37-38 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected invention.

3. The following new grounds of objection and rejection are necessitated by the amendment filed 3/24/03.

4. Claims 22-23 are objected to because said claims drawn to cancel claim 21.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 16-18, 22-26, 30-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for directing the biodistribution of drug to a protein target to an intracellular space upon administration to a host, said method comprising: administering to a mammalian host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of a drug moiety wherein the drug is selected from the group consisting of FK506, cyclosporin and rampamysin and a targeting moiety to an intracellular protein wherein the protein target is FK506 binding protein optionally joined by a linking group, wherein said drug moiety binds to a protein target and said bifunctional molecule has a modulated biodistribution upon administering to said host as compared to a free drug control to direct said biodistribution of said drug to said host to an intracellular space as compared to a free drug control, (2) the said method wherein said bifunctional molecule exhibits enhance efficacy upon administration to said host as compared to a free drug control, (3) the said method wherein said bifunctional molecule exhibits reduced toxicity upon administration to said host as compared to a free drug control, (3) the said method wherein said bifunctional molecule is administered as a pharmaceutical preparation, **does not** reasonably provide enablement for *any* method as set forth in claims 16-18, 22-26, 30-34 and 36 for treating *any* disease. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for directing the biodistribution of drug to a protein target to an intracellular space upon administration to a host, said method comprising: administering to a mammalian host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of a drug moiety wherein the drug is selected from the group consisting of FK506, cyclosporin and rampamysin and a targeting moiety to an intracellular protein wherein the protein target is FK506 binding protein optionally joined by a linking group.

The specification does not teach how to make, much less how to use *any* method as set forth in claims 6-18, 22-26, 30-34 and 36 because there is insufficient guidance as to the structure of *any* "bifunctional molecule less than 5000 dalton", *any* "moiety" comprising *any* "drug", or *any* drug "active derivative thereof" that bind to *any* "protein target", and *any* "intracellular biodistribution modulating protein" for the claimed method of directing the biodistribution of any drug that binds to any protein target to an intracellular space upon administration to a host.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the indefinite number undisclosed drug and "drug analog thereof" that binds to *any* undisclosed protein target in the claimed method, there is insufficient in vivo working example demonstrating that the claimed method could direct the biodistribution of any drug to any

intracellular space since the targeting moiety, the drug, the drug analog thereof and the protein to which said drug and analog thereof bind are not disclosed, much less the bifunctional molecule exhibits enhanced efficacy and/or reduced toxicity upon administration to a host.

Furthermore, the term "having" is open-ended. It expands the "moiety" of the undisclosed drug or active derivative thereof and the targeting moiety in the bifunctional molecule to include additional component other than the linker. There is insufficient guidance as to what are the undisclosed component to be include and whether the resulting bifunctional molecule still maintains its binding specificity toward the undisclosed protein target, in turn, would be useful for a method for directing the biodistribution of the undisclosed drug with enhanced efficacy and reduced toxicity in vivo.

Briesewitz *et al* teach that in general, the creation of unfavorable contacts in a bifunctional molecule that binds to intracellular protein target is far easier to achieve than favorable contacts due to steric hindrance and/or electrostatic repulsion (See page 1956, column 2, in particular). Given the indefinite number of undisclosed bifunctional molecule for the claimed method, it is unpredictable which undisclosed bifunctional molecule would be useful for the claimed method for directing the biodistribution of any drug that binds to any undisclosed protein target as a pharmaceutical preparation.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

7. Claims 16-18, 22-26, 30-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of a method for directing the biodistribution of any drug that binds to any "protein target" to an intracellular space as set forth in claims 6-18, 22-26, 30-34 and 36 because there is inadequately written description about the structure associated with function of any "bifunctional molecule less than 5000 dalton", *any* "moiety" comprising *any* "drug", or *any* drug "active derivative thereof" that bind to *any* "protein target", and *any* "intracellular biodistribution modulating protein" in the claimed method.

The specification discloses only a method for directing the biodistribution of drug to a protein target to an intracellular space upon administration to a host, said method comprising: administering to a mammalian host an effective amount of a bifunctional molecule of less than about 5000 Daltons consisting of a drug moiety wherein the drug is selected from the group consisting of FK506, cyclosporin and rampamysin and a targeting moiety to an intracellular protein wherein the protein target is FK506 binding protein optionally joined by a linking group.

With the exception of the specific method of directing the biodistribution of a drug using the specific bifunctional molecule that bind to the specific intracellular protein, there is insufficient written description about the method using any additional bifunctional molecule comprising *any* additional moiety comprising *any* "drug active derivative that binds to *any* "protein target", *any* "intracellular proteins" or any "intracellular protein" and *any* targeting moiety that optionally joined by any linking group in the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "said moiety" in claim 16 has no antecedent basis because the word "moiety" is not recited in the preamble of claim 16. The word "said" refers to the second iteration of the word "moiety" that appears in the claim before or any where in the claim.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 16-18, 22-26, 30-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pichon *et al* (of record, Mole Pharmacology 51(3): 431-38; 1997; PTO 892) in view of Briesewitz *et al* (Proc Natl. Acad Sci USA 96: 1953-58, March 1998; PTO 892), US Pat No. 5,830,462 (of record, Nov 1998, PTO 1449) and WO 95/10302 publication (of record, April 1995, PTO 1449).

Pichon *et al* teach a method for directing the biodistribution of a drug such as ODN-p-KDEL to an intracellular space such as the internal compartments containing the KDEL receptor, i.e. IC, the ER and the cis-Golgi apparatus (See page 434, Intracellular Localization, in particular). The reference bifunctional molecule consisting of a drug such as ODN which is a 25mer polynucleotide and a targeting moiety such as KDEL that is linked through a linker group such as a thio-carboxymethyl group which forms a thioester bond between said drug and said

targeting moiety (See age 432, Materials and Methods, in particular). The reference bifunctional molecule exhibits enhanced efficacy by 5 fold upon administration to a mammalian host such as human hepatoma HepG2 cells (See page 433, Results, Biological Effect, in particular). The reference drug target is a protein such as the KDEL receptor. The reference bifunctional molecule is administered as a pharmaceutical preparation to inhibit expression of specific genes within cells and as a therapeutic agent for HIV in human (See page 431 and references 10-11 therein, in particular). The reference bifunctional molecule ODN-p-KDEL is a small molecule such as 15 peptides in length, which inherently is less than about 5000 Daltons (See page 432, oligonucleopeptide, in particular). The reference targeting moiety binds to an endogenous biodistribution modulating protein such as the KDEL receptor, which is also an intracellular protein located in the IC, the ER and the cis-Golgi apparatus (See page 434, Intracellular Localization, in particular).

The claimed invention in claim 16 differs from the teachings of the reference only that the method wherein the biodistribution of a drug wherein the drug moiety binds to a protein target and a targeting moiety direct the distribution of said drug to an intracellular space as compared to a free drug control.

The claimed invention in claim 17 differs from the teachings of the reference only that the method wherein the bifunctional molecule exhibits enhanced efficacy upon administration to a host as compared to a free drug control.

The claimed invention in claim 18 differs from the teachings of the reference only that the method wherein the bifunctional molecule exhibits reduced toxicity upon administration to a host as compared to a free drug control.

The claimed invention in claim 19 differs from the teachings of the reference only that the method wherein the bifunctional molecule comprises a linking group.

The claimed invention in claim 20 differs from the teachings of the reference only that the method wherein the bifunctional molecule exhibits enhanced efficacy upon administration to a host as compared to a free drug control.

The claimed invention in claim 30 differs from the teachings of the reference only that the method of administering a drug to a host in need of said drug comprising administering to said host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug moiety comprising said drug or a dirivative thereof covalently linked either directly or through an optional linking group to a targeting moiety that binds to an

intracellular biodistribution modulating protein, wherein said drug moiety binds to an intracellular protein

The claimed invention in claim 34 differs from the teachings of the reference only that the method of administering a drug to a host in need of said drug comprising administering to said host an effective amount of a bifunctional molecule of less than about 5000 daltons consisting of said drug moiety comprising said drug or a derivative thereof covalently linked either directly or through an optional linking group to a targeting moiety that binds to an intracellular biodistribution modulating protein, wherein said drug moiety binds to an intracellular protein and said targeting moiety binds to an endogenous biodistribution modulating protein.

Briesewitz *et al* teach a bifunctional molecule comprising a drug such as FK506, cyclosporin or rapamycin that binds to a protein target such as FKBP12, cyclophilin and FRAP, respectively, and a targeting moiety such as Fyn tyrosine kinase SH2 domain SIQA-LVVP that binds peptides and protein that contain phosphotyrosine residues to direct the biodistribution of the reference molecule to the intracellular space such as cytoplasm via a linker such as the C21 allyl group of FK506 (See page 1953, column 2, second paragraph, and Fig 1, in particular). The reference bifunctional molecule such as FKpYEEI plus Fyn SH domain enhances the affinity by three fold over the natural peptide (See Table 1, Figure 3, page 1955, column 1, first full paragraph, in particular) with inherently reduced toxicity since favorable protein-protein interaction enhances the specificity of the molecule since the IC50 is 750 nM in the absence of FKBP52, which is lowered to an IC250 nM in the presence of FKBP52 (See page 1955, column 1, first full paragraph, page 1957, column 1, in particular).

The '462 patent teaches various drug moiety such as FK506 that are small in size and binds to the endogenous biodistribution modulating protein such as peptidyl prolyl isomerase (FKBP12) or FKBP receptor which is an intracellular protein (See column 22, lines 62-64, in particular). The '462 patent further teaches other drug moiety such as cyclosporin A that binds to the cyclophilin receptor, the estrogen that binds with the estrogen receptor, the vitamin D that binds to the vitamin D receptor with high affinity (See column 22 lines 66-67 bridging column 23, line 1-27). The reference drug moiety such as FK506 is typically being at least about 150 D and few than about 5 kD, usually fewer than about 3 kD (See column 22, lines 62-64, in particular). The '462 patent teaches a targeting domain such as tyrosine kinase CD3 in the bifunctional molecule such as a tyrosine kinase CD3ζ fused to FKBP12 (See Fig 2, in particular) or the DNA binding domain (Gal4) fused to FK506 (See Abstract, Fig 2, column 17, line 14;

column 21 line 23-26, in particular). The '462 patent further teaches that these moiety are linked together through a linking group (See column 24, lines 17-24, column 25, line 28-35, in particular). The '462 patent further teaches a pharmaceutical composition (See column 6, line 63-67 bridging column 7 lines 1-16, in particular). The '462 patent also teaches chimeric protein can be target to a specific location by adding a signal sequence from the vesicle or golgi or ER which are intracellular space, for example (See claim 42 of '462, in particular). The '462 patent teaches the advantages of cyclosporin A2 and FK506 are they bind to their receptor with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular).

The WO 95/10302 publication teaches that linking any drug to a targeting moiety could modulate the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, Summary of the Invention, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the drug moiety in the bifunctional molecule such as the ODN in the ODN-p-KDEL as taught by Pichon *et al* for the FK506 in the FK-pYEEI bifunctional molecule as taught by Briesewitz *et al* or the '462 patent for a method of directing the biodistribution of a drug that binds to a protein target to an intracellular space upon administration to a host as taught by Pichon *et al*, Briesewitz *et al* the '462 patent and the WO 95/10302 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. While the reference is silence with regard to compared the drug to a free drug control, it is within the purview of one ordinary skill in the art to establish the effectiveness of a drug by comparing to the control.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to substitute the drug moiety or the targeting moiety of any bifunctional molecule because the '462 patent teaches that targeting moiety such as FK506 binds to FKBP12 with high affinity Kd $\leq 10^{-8}$ M (See column 23, line 11, in particular); cyclosporin A binds to the cyclophilin receptor with high affinity (See column 27, lines 52, in particular) and like FK1012s, it is neither immunosuppressive nor toxic (See column 27, lines 65-66, in particular). Briesewitz *et al* teach that drugs such as cyclosporin and FK506 are presented by cyclophilin and human FK506 binding protein to inhibit the activity of a calcineurin. By themselves, FK506 and cyclosporin have no measurable affinity for calcineurin. The specificity

and affinity of a ligand protein interaction could be modulated by chemically lining a ligand for an abundant cytosolic protein such as FKBP12 via chemical linkers of different lengths and biofunctional molecule is useful to modulate the potency and specificity of biologically active compounds (See page 1953, column 2, first full paragraph, in particular). The WO 95/10302 publication teaches that linking any drug to a targeting moiety could modulate the volume of distribution of the drug to ovoid non-specific undesired side-effects (See Abstract, Summary of the Invention, in particular).

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
June 11, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600